Intravenous immunoglobulin treatment for long COVID: a case report of clinical and immunological findings

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A previously healthy 39-year-old man developed highly symptomatic post-COVID-19 condition (also known as long COVID) marked by cognitive dysfunction, disabling fatigue, and autonomic symptoms unresponsive to multiple multidisciplinary interventions. Given the presence of markedly elevated serum autoantibodies against G protein-coupled receptors, high-dose intravenous immunoglobulin therapy was initiated at 400 mg/kg per day for 5 consecutive days. After 4 weeks, a maintenance dose of 500 mg/kg was administered for 1 day, followed by two further maintenance cycles consisting of 500 mg/kg per day for 3 consecutive days, each given at 4-week intervals. In parallel, the patient underwent a cognitive stimulation intervention. Neurological symptoms were assessed with the Fatigue Assessment Scale and the WHO Disability Assessment Schedule 2.0, and the immunological profile was longitudinally analysed during intravenous immunoglobulin treatment. Fatigue scores normalised, neurocognitive performance returned to normal value, and quality of life improved after the first infusion and fully recovered within 1 year. Immunological profiling revealed the presence of an inverted CD4 to CD8 T-cell ratio that persisted during the whole follow-up. We also identified a $CD8^+$ T cell–monocyte complex and spontaneous IFNγ release. Intravenous immunoglobulin therapy was associated with a significant reduction of these complexes, spontaneous IFNγ and TNF production, markers of endothelial inflammation, and circulating autoantibody titres. This patient provides exploratory evidence that high-dose intravenous immunoglobulin was associated with sustained clinical recovery from long COVID over 1 year of follow-up, accompanied by immunological changes consistent with modulation of post-viral immune dysregulation, including a reduction in pathogenic T cell–monocyte synapses. Although causal inference cannot be established from a single patient, these findings suggest that this cellular interaction can contribute to long COVID and that immunomodulation could represent a rational therapeutic approach to be evaluated in selected patients.

Introduction

Post-COVID-19 condition (also known as long COVID) or post-acute sequelae of SARS-CoV-2 infection (PASC) affects an estimated 6% of individuals after acute infection,[1] with some studies suggesting higher prevalence,[2] resulting in persistent multisystem symptoms and substantial morbidity. Long COVID is a disease burden not only in adults but also in the paediatric population.[3] Although increasing evidence supports a biological basis for the disease, diagnosis remains clinical and there is no clear consensus definition.[4,5] Pathogenic mechanisms are only partly elucidated, resulting in the absence of approved pharmacological treatments. Disease heterogeneity, spanning clinical phenotypes and immune profiles, further complicates the identification of diagnostic biomarkers and effective therapeutic targets. Immune dysregulation has been proposed as a contributing mechanism in a subset of patients.[6,7] Reported abnormalities include persistent low-grade immune activation, alterations in T-cell and B-cell compartments, dysregulated cytokine signalling, and features suggestive of immune exhaustion.[8–12] In addition, antibody-mediated mechanisms, including the presence of functional autoantibodies targeting G protein-coupled receptors, have been described in long COVID and related post-acute infection syndromes, where they have been associated with symptom burden.[13–16] Other proposed contributors include impaired interferon signalling, persistence of viral antigens, monocyte and macrophage activation, endothelial dysfunction, complement activation, mitochondrial impairment, hypothalamic–pituitary–adrenal axis dysregulation, and vagal nerve dysfunction.[17–23] Collectively, these observations support the concept of long COVID as a condition characterised by chronic immune dysregulation, overlapping with other post-acute infection syndromes.[13]

Intravenous immunoglobulin therapy, known for its broad immunomodulatory effects in autoimmune and post-infectious disorders,[24] has been explored as a potential therapeutic option in long COVID, with preliminary reports suggesting clinical benefit in selected patients.[7,25,26] However, the immunological mechanisms underlying intravenous immunoglobulin responsiveness in this context remain poorly defined.

In this Grand Round, we present a clinically anchored case of highly symptomatic, refractory long COVID treated with high-dose intravenous immunoglobulin, with longitudinal clinical, immunological, and neurocognitive assessments to explore biological correlates of treatment response and to generate mechanistic insights relevant to post-viral immune dysregulation.

Case report

Case presentation

On May 18, 2024, a White man aged 39 years, who was a lifelong competitive athlete, noted symptoms including 1-day fever followed by severe asthenia, easy fatigability, and a dry cough, which he reported to his

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primary care physician 1 week later. His medical history included a duodenal ulcer at age 14 years, for which he receives pantoprazole twice yearly during symptom flares, and a right inguinal hernia repair when he was age 4 years. He had received three doses of SARS-CoV-2 vaccine since 2021 (two AstraZeneca doses on March 4, 2021, and May 24, 2021, and one Pfizer dose on Dec 2, 2021). He developed acute SARS-CoV-2 infection on May 1, 2023, and again on Dec 13, 2023, diagnosed by a positive SARS-CoV-2 antigen test in both instances; both episodes were characterised by high fever, general malaise, and rhinitis. The second infection was followed by a prolonged convalescence lasting more than 1 month, characterised by persistent asthenia and arthromyalgia.

Due to ongoing and worsening symptoms, the primary care physician ordered blood tests, chest radiography, transthoracic echocardiography, ear, nose, and throat evaluation, and neurological examination, which were done between May and July, 2024, all of which were unremarkable. His symptoms progressively worsened, with the onset of daytime hypersomnia and nocturnal insomnia, concentration and memory difficulties, brain fog, photophobia, psychomotor slowing, dysesthesias, orthostatic hypotension, palpitations, worsening headaches, and cold intolerance despite the summer season. On June 21, 2024, he was admitted to the neurology department of a tertiary care hospital in Rome, Italy. Brain MRI with contrast, electromyography, electroneurography, and lumbar puncture showed no significant abnormalities. A 24-h electrocardiogram, recorded with a Holter monitor, was unremarkable, whereas an exercise stress test revealed a moderate reduction in cardiopulmonary capacity. Lymphocyte subpopulation analysis showed an inverted CD4 to CD8 T-cell ratio (CD4 25·5%, CD8 63·2%; normal range CD4 44·3%, CD8 23·4%). Baseline autoimmune and inflammatory laboratory tests included erythrocyte sedimentation rate, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibodies, extractable nuclear antigen panel, cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies, and complement concentrations as well as coeliac disease screening, all of which were within the normal range. Serologies for *Borrelia* spp and HIV were negative. During hospitalisation, a positive herpes simplex virus type 1 (HSV-1) IgM result prompted administration of a 1-day course of intravenous aciclovir, which produced a transient improvement in neurocognitive symptoms, while other symptoms persisted. However, HSV-1 IgG seroconversion was never documented, suggesting a non-specific finding. After all diagnostic investigations had been completed, the patient was deemed suitable for outpatient follow-up and was discharged on June 28, 2024. 7 days after discharge, his primary care physician prescribed a 21-day course of aciclovir therapy due to worsening of headache, fatigue, and insomnia; this therapy again improved cognitive symptoms but had no effect on headaches, fatigue, arthromyalgia, or insomnia.

The patient reported that as of May 18, 2024, he had experienced a marked decline in quality of life, reducing his doctoral research (his only employment) to 3 days per week with substantial loss of productivity. He was unable to watch a full film because of impaired concentration and fatigue, and he could tolerate only light activity (about 20 min of yoga). Without a definitive diagnosis, the patient underwent several treatments from May to September, 2024, prescribed by different physicians or self-initiated attempts, rather than a single coordinated therapeutic plan. Ozone therapy was carried out for 1 month, with at least two sessions per week. Vagal nerve stimulation was performed in the evenings for 5 months. Vitamin supplements were taken for 2 months, melatonin for 8 months, and glutathione for 1 month. Pharmacological treatments and dietary supplements partially overlapped with periods of ozone therapy or vagal nerve stimulation. These treatments provided only minimal and transient benefit, and were therefore discontinued.

On Sept 19, 2024, because of persisting symptoms, the patient received a diagnosis of long COVID from a physician and was therefore referred to the long COVID clinic of the National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS (Rome, Italy) where he attended on Oct 22, 2024 as an outpatient and where further evaluations were completed. Thyroid-stimulating hormone concentrations were normal (normal range 0·4–3·5 µU/mL) and morning cortisol measured 12 µg/dL (normal range 4·3–22·4 µg/dL), a value warranting an adrenocorticotropic hormone stimulation test to exclude diagnosis of adrenal insufficiency; the adrenocorticotropic hormone stimulation test showed an appropriate cortisol response (1 µg; adrenal insufficiency was defined as basal <3 µg/dL or peak <18 µg/dL).

Investigation and treatment

Consistent with our pathogenetic model of vagus nerve, hypothalamic–pituitary–adrenal axis, and mitochondrial system dysfunction, in which acetylcholine and noradrenaline are key mediators,[21] we assessed autoantibodies against G protein-coupled receptors—including AT1R, ETAR, adrenergic (α1, α2, β1, and β2), and muscarinic (M1–M5) receptors—which were markedly elevated. Autoantibodies were measured with ELISA technology (CellTrend, Luckenwalde, Germany[27]). Upper normal limits were established based on validation studies in a healthy control group and defined as values exceeding the 95th percentile and were commercialised for research purposes. Given the severity of symptoms, the absence of contraindications (ie, IgA 2·39 g/L), and the evidence of immune dysregulation, we planned off-label intravenous immunoglobulin therapy: 400 mg/kg per day for 5 days, followed by a maintenance dose of 500 mg/kg every 3 weeks for five further infusions, with the possibility to

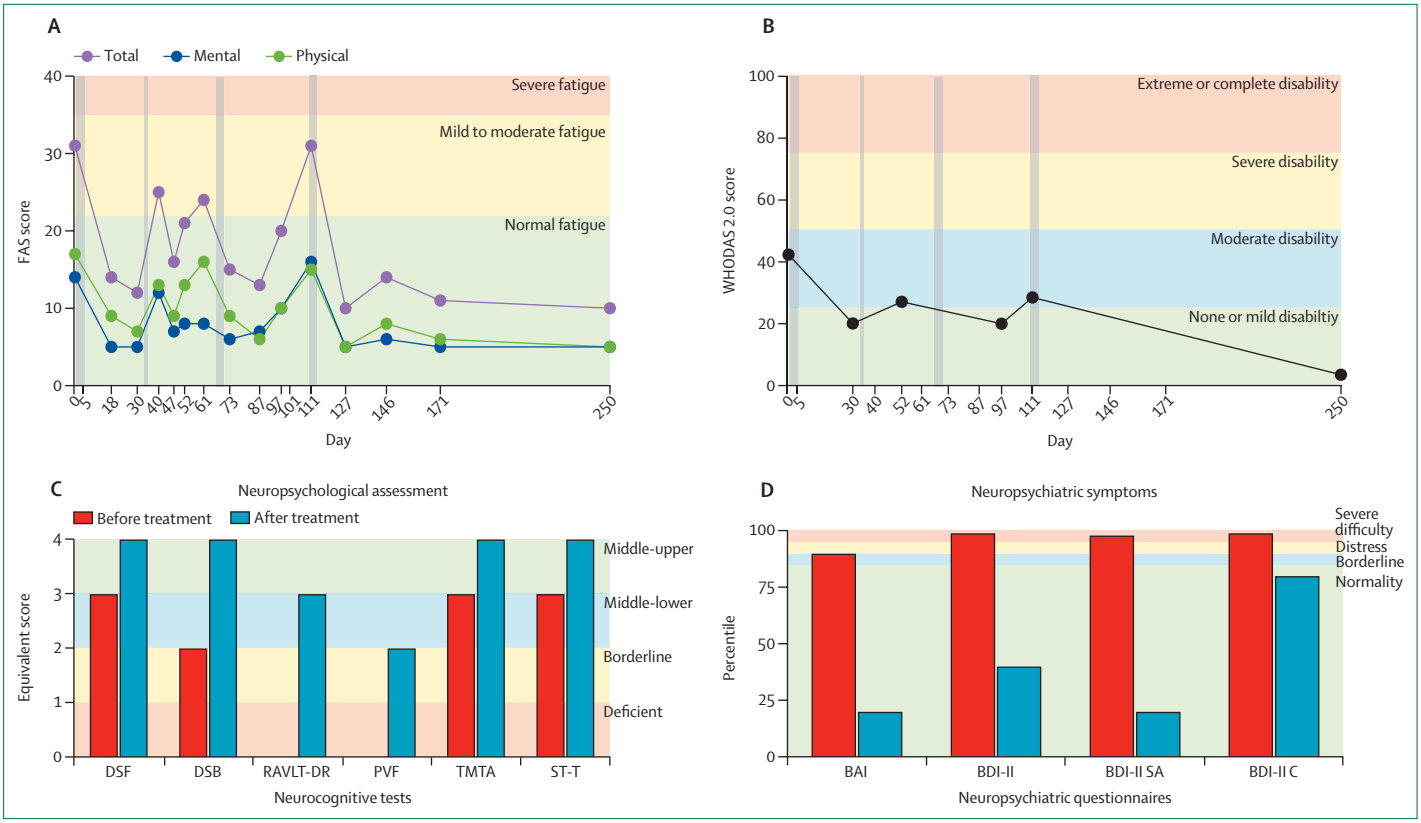

***Figure 1*: FAS, WHODAS 2.0, and neuropsychological trajectories over time**
Day 0 is Feb 7, 2025, the day before the first infusion. Grey-shaded areas indicate intravenous immunoglobulin treatment cycles. (A) Total FAS score results from the sum of the physical and mental FAS scores. FAS scores are categorised as: normal fatigue (<22), mild to moderate fatigue (22–34), and severe fatigue (≥35). (B) WHODAS 2.0 scores are categorised as none or mild disability (0·0–24·9), moderate disability (25·0–49·9), severe disability (50·0–74·9), and extreme or complete disability (75·0–100·0). (C) Results of the neuropsychological assessment scores before treatment (Nov 12, 2024) and after treatment (Nov 4, 2025; day 250). Scores are expressed as equivalent scores and are categorised as: deficient performance (0), borderline performance (1), middle-lower performance (2–3), and middle-upper performance (4). (D) Results of the neuropsychiatric symptoms assessed before treatment (Nov 12, 2024) and after treatment (Nov 4, 2025; day 250). Scores are expressed as percentiles and categorised as: normality (<85th percentile), borderline (85–90th), distress (91–95th), and severe difficulty (>95th). BAI=Beck Anxiety Inventory. BDI-II=Beck Depression Inventory. BDI-II C=Beck Depression Inventory Cognitive. BDI-II SA=Beck Depression Inventory Somatic-Affective. DSB=digit span backward. DSF=digit span forward. FAS=Fatigue Assessment Scale. PVF=phonological verbal fluency. RAVLT-DR=Rey Auditory Verbal Learning Test-Delayed Recall. ST-T=Stroop colour-word test–time. TMTA=Trail Making Test A. WHODAS 2.0=WHO Disability Assessment Schedule 2.0.

change dosage and schedule according to the clinical response. The dosage was selected on the basis that doses of 1 g/kg or more exert immunomodulatory effects, which we sought to achieve during the induction phase. The maintenance regimen was informed by the case series reported by Thompson and colleagues.[28] Intravenous immunoglobulin therapy was administered with a single commercial preparation (Privigen, CSL Behring, Bern, Switzerland), a 10% liquid formulation of human normal immunoglobulin containing at least 98% IgG, with IgG subclass distribution comparable to that of normal human plasma.[29] Privigen contains trace amounts of IgA, is stabilised with L-proline, and does not contain preservatives or carbohydrate stabilisers. Clinically significant fatigue, disability, and perceived daily functioning over time were evaluated with the Fatigue Assessment Scale (FAS)[30] normative scores and the normative reference scores for the Italian population in the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0; figure 1).[31] A neurocognitive stimulation programme was initiated concurrently with intravenous immunoglobulin therapy. Neuropsychological profiles were assessed on Nov 12, 2024, approximately 12 weeks before treatment initiation, and on Nov 4, 2025, after 1 year of follow-up (figure 1; appendix p 2). To longitudinally assess the immunological profile (figures 2, 3), plasma and peripheral blood mononuclear cells (PBMCs) were collected on the first day of each intravenous immunoglobulin infusion cycle and monthly during the follow-up period.

See **Online** for appendix

Clinical course

Intravenous immunoglobulin treatment was initiated on Feb 8, 2025 (day 1). On day 10, 5 days after completing the first treatment cycle (days 1–5), the patient had a marked improvement in symptoms, with a rapid resolution of brain fog and a reduction in physical fatigue, as reflected by the FAS (figure 1). A mild recurrence of symptoms occurred approximately 4 weeks after the first treatment

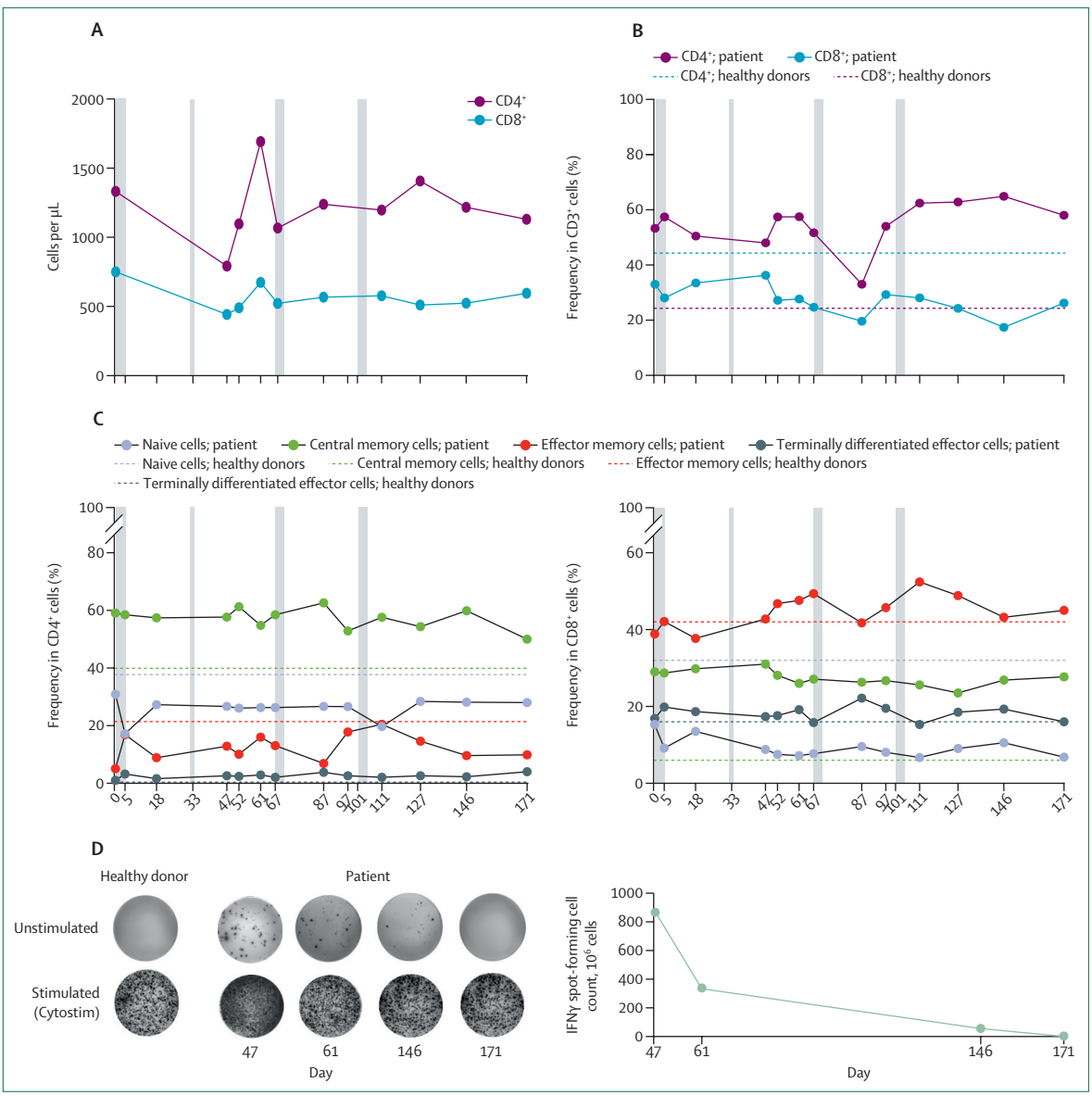

***Figure 2*: Longitudinal immunological and functional monitoring**

Day 0 is Feb 7, 2025, the day before the first infusion. Grey-shaded areas indicate intravenous immunoglobulin treatment cycles. Dotted lines are reference values of healthy donors (n=20). (A–C) Longitudinal analysis of circulating T-cell subsets over the study period. (A) Absolute $CD4^+$ and $CD8^+$ T-cell counts. (B) Frequency of $CD4^+$ and $CD8^+$ T cells among total $CD3^+$ T cells. (C) Distribution of $CD4^+$ and $CD8^+$ T-cell differentiation subsets. Peripheral blood mononuclear cell of patient and healthy donors (n=20) were stained with CD3-APC-AF750, CD4-APC, CD8-APC-A700, CD27-PC7, and CD45RA-FITC. (D) IFNγ ELISpot assay (Mabtech) in unstimulated or stimulated (Cytostim) cells in healthy donors and patient at different timepoints (days 47, 61, 146, and 171). Representative wells and quantification of IFNγ spot-forming cells show a progressive decline in spontaneous release of IFNγ.

cycle, consistent with the intravenous immunoglobulin half-life. After the first maintenance infusion (500 mg/kg on day 33), no clinical benefit was observed. The second (days 67–69) and third (days 101–103) maintenance infusions were therefore administered at 1·5 g/kg over 3 days to maintain immunomodulatory efficacy while minimising the risk of adverse events. After the third maintenance infusion (days 101–103), a transient increase in FAS was observed, coinciding with an intercurrent gastroenteritis. Despite fluctuations in symptoms and physical assessment (within FAS score) in parallel with intravenous immunoglobulin pharmacokinetics, the patient had sustained overall improvement and a gradual reduction in disability over time (figure 1).

On June 3, 2025, a few days after the third maintenance infusion, the patient returned to work and resumed non-competitive sports, with resolution of fatigue, post-exertional malaise, and headache. Given the clinical benefit, the patient elected to discontinue therapy after the third maintenance infusion. Follow-up over the

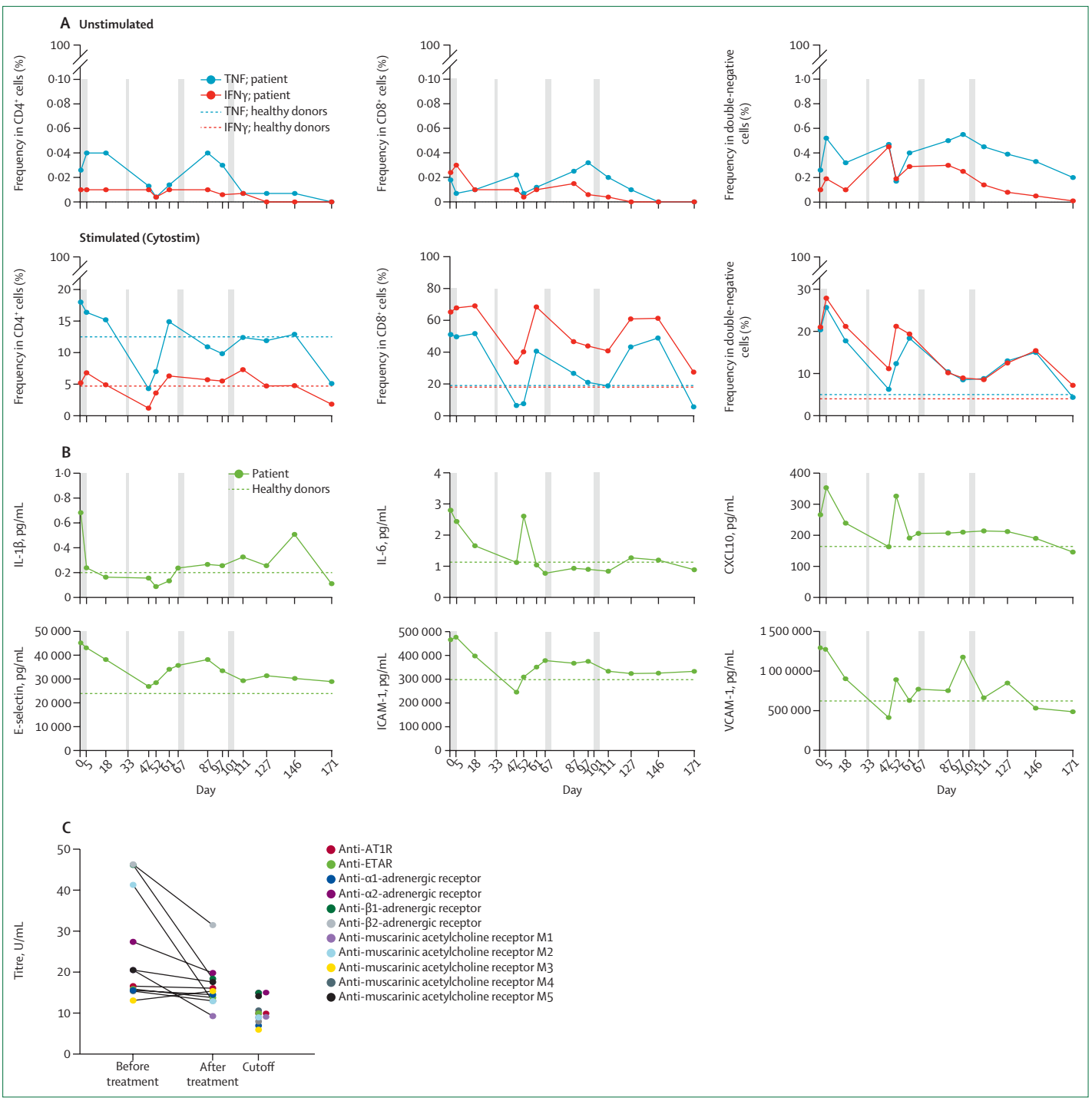

***Figure 3*: Longitudinal cytokine and autoantibody profiling**
Day 0 is Feb 7, 2025, the day before the first infusion. Grey-shaded areas indicate intravenous immunoglobulin treatment cycles. Dotted lines are reference values of healthy donors (n=20). (A) Intracellular cytokine production by T-cell subsets over time. T cells were stained with antibodies specific for surface markers (CD3, CD4, and CD8) and for intracellular cytokines (IFNγ and TNF). Data were acquired on FACS Lyric (Beckton Dickinson, Franklin Lakes, NJ, USA) and analysed through FlowJo version 10.10 (Beckton Dickinson, Franklin Lakes, NJ, USA). (B) Longitudinal analysis of plasmatic mediators (cytokines and markers of endothelial inflammation) was performed by Ella automated immunoassay (Bio-Techne, Minneapolis, MN, USA). (C) Autoantibody titres against neurological and cardiovascular G protein-coupled receptors measured at 90 days before intravenous immunoglobulin treatment and after treatment (day 250). Measurements were performed by CellTrend service. Cutoff values correspond to normal levels of these autoantibodies in the healthy population.

subsequent 9 months showed continued clinical improvement, with a quality of life comparable to before the patient had long COVID. Regarding safety, on day 3, during the first treatment cycle, the patient had mild headache, managed with non-steroidal anti-inflammatory drugs for 1 day, and a superficial thrombophlebitis, which was treated with prophylactic-dose low molecular weight heparin for 1 week. On days 18, 38, and 55, a transient increase in liver aminotransferases (up to twice the upper normal limit) was observed, without associated clinical symptoms.

Neurocognitive assessment and cognitive stimulation intervention

A comprehensive neuropsychological assessment was performed (figure 1; appendix p 2) with a standardised battery of 20 tests across five cognitive domains (ie, memory [episodic verbal memory, short-term memory, and working memory], attention, language, executive functions or constructional praxis, and speed of psychomotor processing). Moreover, specific scales for neuropsychiatric symptoms were also evaluated (figure 1). These tests were performed before the intravenous immunoglobulin treatment (Nov 12, 2024) and after 1 year (Nov 4, 2025; day 250).

Raw neuropsychological assessment scores were adjusted for age, sex, and education level with Italian normative data (corrected score), then converted into equivalent scores according to the Italian standardisation procedure,[32] based on an ordinal scale ranging from 0 to 4: 0 (deficient performance); 1 (borderline performance); 2–3 (middle-lower performance); and 4 (middle-upper performance). The assessment of neuropsychiatric symptoms with Italian normative cutoff scores derived from validated psychometric instruments, are classified as follows: normality (<85th percentile), borderline (85–90th), distress (91–95th), and severe difficulty (>95th).

On Nov 12, 2024, the initial neuropsychological assessment highlighted below-average performance (equivalent scores of 0) in long-term verbal episodic memory and phonological verbal fluency (figure 1; appendix p 2). In addition, clinically significant indicators of anxiety (90th percentile) and depression (99th percentile) were detected, with prominent somatic-affective features (98th percentile) and particularly severe depressive cognitive symptoms (99th percentile; figure 1).

To enhance cognitive performance and improve the patient's emotional and psychological state, a cognitive stimulation programme was initiated on Feb 7, 2024 (day 0), 1 day before initiation of intravenous immunoglobulin treatment. The intervention was delivered using COGPACK (Marker Software, Heidelberg, Germany), a computer-based cognitive training programme including exercises targeting memory, attention, executive functions, and processing speed.[21] Treatment effects were evaluated within the patient across time, rather than by comparison with external normative scores. Four 90-min cognitive stimulation sessions were performed: one before the first intravenous immunoglobulin infusion (on day 0) and three follow-up sessions after each subsequent intravenous immunoglobulin administration (on days 26, 62, and 112). At the end of the cognitive stimulation programme, follow-up neuropsychological and neuropsychiatric symptoms assessments were performed (on Nov 4, 2025; day 250). Results showed significant improvement in long-term verbal episodic memory (equivalent score of 3) and phonological verbal fluency (equivalent score of 2); cognitive performance was in line with that of the normative reference data (adjusted for age, education and gender; figure 1; appendix p 2). Furthermore, symptoms of anxiety and depression had notably improved, with scores within normal limits (20th percentile for Beck Anxiety Inventory, 40th percentile for Beck Depression Inventory Somatic-Affective, and 80th percentile for Beck Depression Inventory Cognitive; figure 1). Detailed results are in the appendix (p 2).

Immunological findings and longitudinal profiling

To assess how intravenous immunoglobulin infusion can affect immune system homoeostasis, we prospectively characterised, as previously described,[33,34] B cells, natural killer cells, and T-cell subsets with peripheral blood samples collected before and after each infusion (on days 0, 5, 18, 47, 52, 61, 67, 87, 97, 111, 127, 146, and 171).

The B-cell and natural killer-cell compartments did not reveal any major quantitative or phenotypic abnormalities when compared with healthy donor (n=20) reference values. By contrast, a marked alteration was observed within the T-cell compartment. Before the infusion, the patient exhibited an inverted CD4 to CD8 T-cell ratio, characterised by a markedly elevated $CD8^+$ T-cell frequency and a reduced $CD4^+$ T-cell frequency, which persisted throughout the entire observation period (from day 0 to day 171; figure 2). The frequency of $CD8^+$ T cells remained consistently elevated (mean 54·7%), significantly higher than in healthy donors (mean 24·3%), whereas $CD4^+$ T cells were lower than in healthy donors (mean 27·3% *vs* 44·3% in healthy donors).

We next analysed the differentiation profile of $CD4^+$ and $CD8^+$ T cells, assessing the relative frequencies of naive cells ($CD45RA^+CCR7^+$), central memory cells ($CD45RA^-CCR7^+$), effector memory cells ($CD45RA^-CCR7^-$), and terminally differentiated effector cells ($CD45RA^+CCR7^-$; figure 2). The $CD4^+$ compartment showed reduced naive T cells and a relative enrichment in central memory cells, suggesting a skewing towards antigen-experienced phenotypes. Strikingly, the $CD8^+$ compartment exhibited a dominance of effector memory and terminally differentiated effector cells, with only a minimal proportion of naive cells, consistent with a chronically activated or antigen-experienced profile. Notably, these alterations remained stable over time, with no clear changes before versus after intravenous immunoglobulin

infusions, indicating that intravenous immunoglobulin did not acutely reshape T-cell differentiation in this patient.

To investigate the functional consequences of the activated T-cell profile, we quantified the ex-vivo pro-inflammatory T-cell signature by performing IFNγ enzyme-linked immunosorbent spot (ELISpot) after T-cell receptor triggering (Cytostim, Miltenyi Biotec, Bergisch Gladbach, Germany) with PBMCs collected at multiple timepoints (days 47, 61, 146, and 171) during intravenous immunoglobulin treatment. As expected, PBMCs from healthy donors did not produce IFNγ in the absence of stimulation (figure 2). By contrast, the patient displayed a high frequency of spontaneously IFNγ-secreting PBMCs, indicating active inflammatory cytokine production (figure 2). Notably, the intravenous immunoglobulin treatment was associated with a reduction of the number of IFNγ spot-forming cells, eventually returning to background concentrations by the final timepoint (day 171; figure 2). Although we recognise that controlled studies are needed to verify the cause–effect relationship of this observation, these data suggest that intravenous immunoglobulin can exert an immunomodulatory effect capable of suppressing aberrant IFNγ production.

Mechanistic immunological interpretation and implications

The immunological findings about the spontaneous cytokine release by T cells in our patient are consistent with mechanistic evidence in long COVID, where Krishna and colleagues[32] showed that spontaneous IFNγ release depends on $CD8^+$ T cells interacting with $CD14^+$ monocytes. In this study, depletion of $CD14^+$ cells by magnetic activating cell sorting abolished IFNγ production, although monocytes themselves were not the source of IFNγ, confirming that $CD8^+$ T cells are the primary producers in an activation-permissive myeloid environment.[32] Other previous work has shown that T cell–monocyte complexes can form in chronic or hyperinflammatory immune states, including HIV infection,[35] tuberculosis, and dengue,[36] where they display unique activation signatures and support sustained T-cell stimulation.

To investigate whether a similar phenomenon was present in our patient, we quantified circulating T cell–monocyte complexes by flow cytometry. On day 47, when spontaneous IFNγ secretion was high, 2·15% of $CD45^+$ cells consisted of $CD3^+CD14^+$ cells (appendix p 3). These complexes were mostly $CD8^+$ (appendix p 3) and showed very high forward scatter area (FSC-A) and side scatter area (SSC-A), consistent with a doublet composed of a lymphocyte and a monocyte (appendix p 3). After sorting, the two cell populations became physically separated, as shown by the appearance of distinct lymphocyte and monocyte clusters and the loss of the high ratio of FSC-A to SSC-A signature (appendix p 3). Phenotypically, T cells within the complexes were predominantly $CD8^+$ (80%), with a proportion of double-negative T cells (15%).

To evaluate the link between T cell–monocyte complexes and inflammation, we analysed a later timepoint (day 171), after spontaneous IFNγ release had resolved. The frequency of complexes dropped to 0·47%, a level comparable to healthy donors (0·73%; appendix p 3), supporting the association between T cell–monocyte interactions and spontaneous IFNγ production.

To further characterise the inflammatory profile associated with the patient's disease course, we performed longitudinal functional analysis of T cells,[34] assessing IFNγ and TNF production in $CD4^+$, $CD8^+$, and double-negative T cells. The functional competence was assessed both in resting (unstimulated) and polyclonal activated T cells (figure 3).

At baseline and during the early timepoints, the patient exhibited markedly elevated spontaneous IFNγ and TNF production, particularly within unstimulated $CD8^+$ and double-negative T-cell subsets, whereas healthy donors displayed minimal to undetectable cytokine release under the same conditions. These data indicate a chronic, antigen-independent activation of $CD8^+$ and double-negative T cells, consistent with spontaneous ELISpot activity and the expansion of effector $CD8^+$ T cells. Moreover, polyclonal T-cell receptor triggering induced a stronger T-cell response in terms of IFNγ and TNF production compared with healthy donors.

After each intravenous immunoglobulin infusion, a clear and reproducible reduction of inflammatory cytokine production of both resting and stimulated cells was observed across all T-cell compartments. Each infusion was associated with a decline in IFNγ and TNF secretion, suggesting a possible direct and rapid immunomodulatory effect of intravenous immunoglobulin on hyperactivated T cells. Notably, the absence of cytokine reduction coincided with the second infusion, which was administered at a lower dose, raising questions about the optimal dose required to reach effective immunomodulation.

Together, our data indicate that $CD8^+$ and double-negative T cells are major contributors to the exaggerated inflammatory cytokine environment in this patient, and that intravenous immunoglobulin therapy could potentially dampen both spontaneous and activation-induced cytokine release, in a dose-dependent manner.

We therefore analysed the effect of the intravenous immunoglobulin therapy on other inflammatory and endothelial dysfunction markers, known to play a role in long COVID. By use of the Ella platform (Bio-Techne, Minneapolis, MN, USA), we measured IL-1β, IL-6, CXCL10, and the endothelial adhesion molecules E-selectin, ICAM-1, and VCAM-1 in longitudinal plasma samples (figure 3). At baseline (day 0), the patient displayed elevated concentrations of pro-inflammatory cytokines and high concentrations of endothelial activation markers, consistent with a sustained

inflammatory state and ongoing endothelial involvement. Intravenous immunoglobulin treatment was associated with a progressive decline in inflammatory cytokines, with values returning to the normal range by day 171 (cytokines were measured on days 0, 5, 18, 47, 52, 61, 67, 87, 97, 111, 127, 146, and 171). This decline included a marked reduction of IL-1β and CXCL10, both of which are correlated with persistent symptoms and interferon-associated immune activation in long COVID.[37,38] IL-6 concentrations also decreased after the second maintenance infusion (day 33), with minor fluctuations during the follow-up period (figure 3). In parallel, intravenous immunoglobulin exerted a measurable effect on the endothelium: concentrations of E-selectin, ICAM-1, and VCAM-1 consistently diminished over the course of treatment, indicating reduced endothelial activation and vascular inflammation (figure 3).

Autoantibody concentrations were assessed against G protein-coupled receptors, including AT1R, endothelin receptors A, α1-adrenergic receptors, α2-adrenergic receptors, β1-adrenergic receptors, β2-adrenergic receptors, and muscarinic acetylcholine receptors M3–M5.

Among these autoantibodies, β2-adrenergic receptor antibodies are known to exert both anti-inflammatory and immunomodulatory effects on innate[39] and adaptive[40] immune cells, partly through enhancement of T-cell activation.[41] Accordingly, antibodies that impair β2-adrenergic receptor signalling can disrupt this regulatory balance, contributing to chronic inflammation, autonomic dysfunction, and multisystem symptoms.[41]

In our patient, β2-adrenergic receptor autoantibody concentrations were markedly elevated 12 weeks before intravenous immunoglobulin. Although they remained above the cutoff value (95th percentile of a healthy population),[27] intravenous immunoglobulin therapy was associated with a substantial overall reduction in β2-adrenergic receptor concentrations, consistent with the downward trend observed for the other G protein-coupled receptor autoantibodies (figure 3).

Notably, each intravenous immunoglobulin infusion was followed by a downward shift in inflammatory markers, with the only exception occurring after the low-dose second infusion, during which the cytokine and adhesion-molecule profile did not improve. Full-dose infusions restored the downward trend, suggesting a dose-dependent effect of intravenous immunoglobulin on controlling vascular and immune inflammation.

Together, these findings support a model in which intravenous immunoglobulin can dampen both systemic cytokine production and endothelial activation, complementing our cellular observations (ie, spontaneous IFNγ release, CD8 expansion, and T cell–monocyte complexes) and pointing to endothelium-centred immune dysregulation as a key component of the patient's long COVID pathology.

Current evidence on intravenous immunoglobulin therapy for long COVID and its putative mechanisms of action

Intravenous immunoglobulin is a therapeutic preparation of pooled IgG antibodies purified from the plasma of thousands of healthy donors.[42,43] It contains a broad spectrum of antibodies that mirror the normal human antibody repertoire and is administered intravenously to provide passive immunity or to modulate immune responses.[42,43]

When administered at doses greater than 1 g/kg, intravenous immunoglobulin exerts pleiotropic immunomodulatory effects, including neutralisation of pathogenic autoantibodies, modulation of Fc receptor and complement activity, interference with cytokine networks, and expansion of regulatory T cells and B cells.[43,44] Moreover, recent evidence indicates that intravenous immunoglobulin can reprogramme immune responses towards an anti-inflammatory state by modulating Fc-dependent and $F(ab')_2$-dependent mechanisms.[45] Intravenous immunoglobulin is also an established therapy for several neuroimmune and inflammatory diseases, including Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, immune thrombocytopenia, and Kawasaki disease.[46–48]

Intravenous immunoglobulin has also been implemented in post-acute infection syndromes. A case series described resolution of parvovirus B19-associated post-viral syndrome after intravenous immunoglobulin therapy, with a durable long-term response.[49] Evidence regarding the use of intravenous immunoglobulin therapy in adolescents and adults with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a condition that substantially overlaps with long COVID,[50] derives from four double-blind randomised controlled trials, the results of which are conflicting.[51–54] Although the scientific rationale is promising,[24] evidence on the use of intravenous immunoglobulin in long COVID currently derives only from an uncontrolled case series of six patients treated with intravenous immunoglobulin at a dose of 500 mg/kg once every 2 weeks (400 mg/kg once every 2 weeks for one participant), all showing documented immune dysregulation, such as altered immunoglobulin subclass distribution or lymphocyte subset imbalance, treated for 6–12 months depending on the patient's clinical response.[28] All patients showed sustained clinical improvement over time, particularly in fatigue, cognitive impairment, and dysautonomia, with an excellent safety profile.[28] Nevertheless, no evidence regarding the effect on immune cell homoeostasis has been identified. Reports of G protein-coupled receptor-autoantibody neutralisation with rovunaptabin (BC-007)[55] and immunoadsorption in post-COVID-19 cohorts suggest that reducing pathogenic autoantibodies could be associated with symptomatic improvement, suggesting a potential pathogenic role for these

antibodies in long COVID.[56] Although evidence remains scarce and comparative data are low quality, no comparable clinical responses were reported in a long COVID case series,[28] in which patients received low-dose (500 mg/kg) intravenous immunoglobulin for more than 6 months, nor in ME/CFS studies using low-dose intravenous immunoglobulin.[51–54] Together with the favourable outcome observed in this patient, these observations suggest, without establishing causality, that high-dose intravenous immunoglobulin (>1 g/kg) can be relevant to clinical response in some patients.[43,44] This finding warrants evaluation in controlled studies. Given that intravenous immunoglobulin consists predominantly of IgG, the infused antibodies could saturate Fcγ receptors on monocytes, thereby increasing their activation threshold[57] and hindering the formation of stable immunological synapses with $CD8^+$ T cells. This Fcγ receptor-mediated blockade could be a key mechanism through which intravenous immunoglobulin dampens chronic T cell–monocyte crosstalk in post-viral immune dysregulation.

Beyond Fcγ receptor saturation, intravenous immunoglobulin exerts broad immunomodulatory effects on the innate and adaptive immune systems through multiple mechanisms: suppressing monocyte and macrophage activation;[58] promoting anti-inflammatory cytokines while reducing pro-inflammatory mediators;[59,60] inhibiting apoptosis via sequestration of Fas ligand;[61] and downregulating cytokine-induced expression of endothelial adhesion molecules such as ICAM-1 and VCAM-1.[62] By modulating endothelial adhesion and leukocyte trafficking, intravenous immunoglobulin can further prevent immune cell extravasation and perpetuation of tissue inflammation. Several additional pathways likely converge to amplify these effects. High-dose intravenous immunoglobulin saturates the neonatal Fc receptor (FcRn), a key recycling receptor expressed by endothelial cells that extends IgG half-life; overwhelming this pathway accelerates the degradation of endogenous IgG, including pathogenic autoantibodies. Indeed, in the absence of FcRn, the half-life of IgG is dramatically shortened, effectively preventing the initiation and propagation of tissue inflammation.[63] Furthermore, sialylated IgG Fc fractions within intravenous immunoglobulin can upregulate the inhibitory FcγRIIb, shifting the immunoregulatory balance towards suppression, while concurrent saturation of activating Fcγ receptors diminishes their availability for immune-complex binding and downstream activation.[64] Interestingly, intravenous immunoglobulin has been shown to modulate metabolic pathways in PBMCs, consistent with restoration of anti-inflammatory mechanisms.[45] Finally, evidence from patients with immune thrombocytopenia indicates that intravenous immunoglobulin rapidly down-modulates type I interferon-stimulated gene expression, leading to reduced FcγRIII amounts on monocytes and further altering the balance between activating and inhibitory Fcγ receptors.[65]

Long COVID is not only a disease burden in adults but also affects the paediatric population,[66] highlighting the urgent need for dedicated paediatric long COVID research to develop effective diagnostic and therapeutic strategies. Children with long COVID also showed a distinct pro-inflammatory signature, consistent with observations in adults; the overexpression of inflammatory cytokines compared with healthy control participants further supports immune dysregulation and chronic inflammation as key features across age groups.[3] Given this shared immunopathology, intravenous immunoglobulin is also a potential therapeutic option for children with long COVID. Randomised clinical trials are needed to show therapeutic efficacy and establish the optimal therapeutic dose, administration schedule, and appropriate patient selection criteria. Comparative and controlled investigations assessing different intravenous immunoglobulin preparations will be necessary to delineate formulation-specific immunomodulatory effects, optimise dosing strategies, and refine patient selection in post-acute infection syndromes and long COVID. Currently, two randomised, placebo-controlled clinical trials are evaluating the efficacy of intravenous immunoglobulin in patients with long COVID. The RECOVER-AUTONOMIC trial (NCT06305780) is a multicentre, adaptive platform study sponsored by the US National Institutes of Health that compares multiple interventions for postural orthostatic tachycardia syndrome. The IN-PASC trial (NCT05350774) is currently enrolling patients with long COVID presenting with neurological symptoms, assessing the potential therapeutic role of intravenous immunoglobulin compared with placebo. No interim analyses from these studies are currently available. The results of these ongoing trials will be crucial to establish whether intravenous immunoglobulin can effectively restore immune homoeostasis in long COVID. Both trials, in our opinion, could narrow the spectrum of patients considered eligible for immunomodulatory therapies. The results from the patient discussed in this Grand Round suggest that immune-mediated mechanisms extending beyond autonomic and neurological dysfunction alone could be clinically relevant. In this context, the assessment of autoantibodies targeting G protein-coupled receptors can help identify patients most likely to benefit from intravenous immunoglobulin therapy, although the relevant antibody profiles remain unclear. In addition, aberrant immune cell interactions, such as the pathological $CD8^+$ T cell–monocyte complexes observed in this patient, warrant further investigation as potential biomarkers of treatment eligibility and therapeutic response. Together, these observations highlight the biological heterogeneity of long COVID and support the development of biomarker-guided approaches in future interventional studies.

Conclusions

We report treatment of a patient with long COVID with initial daily intravenous immunoglobulin (500 mg/kg) for 5 days followed by a 1-day maintenance infusion of 500 mg/kg after a month, and two further maintenance infusions of 500 mg/kg per day for 3 consecutive days, each given at 4-week intervals supported by detailed immunological and neurocognitive characterisation with follow-up of approximately 12 months. Intravenous immunoglobulin administration was associated with rapid clinical improvement, including resolution of fatigue and cognitive symptoms and recovery of functional status, alongside immunological changes consistent with restoration of immune homoeostasis. These changes included a reduction in aberrant $CD8^+$ T cells–monocyte synapses associated with spontaneous IFNγ release and endothelial inflammation, offering a plausible biological context for the observed clinical response. Our study identifies the $CD8^+$ T cell–monocyte complexes as a potential contributor to post-viral immune dysregulation and a candidate biomarker and therapeutic targeting long COVID. Furthermore, this case report highlights the potential value of screening for autoantibodies directed against G protein-coupled receptors in patients with long COVID. In this patient, intravenous immunoglobulin was associated with a progressive decrease in circulating antibodies targeting G protein-coupled receptors, particularly those involved in neurotransmission and vascular regulation.[14,15]

The durability of treatment responses, and the effect of re-infection or vaccination on long COVID remain unknown and require controlled studies with longer follow-up. Some clinical data suggest a possible detrimental role of re-infection,[67,68] whereas SARS-CoV-2 vaccination appears to be associated with clinical improvement.[69,70]

Search strategy and selection criteria

We searched PubMed from database inception to Nov, 12, 2025, using combinations of the following keywords: "long COVID", "post-COVID condition", "post-acute sequelae of SARS-CoV-2 infection", "PASC", "intravenous immunoglobulin", "immune system", "lymphocytes", "monocytes", "T-cells", "IFN-γ", "G-protein–coupled membrane receptors", "GPCR", "post-acute infection syndrome", "PAIS", "neuro-cognitive dysfunction", "neuropsychological assessment", "fatigue", "immunomodulation", "autoantibodies", "β2-adrenergic receptors", "myalgic encephalomyelitis/chronic fatigue syndrome", and "clinical trial". We included all review articles, commentaries, original research articles, guidelines, case series, case reports, and registered trial protocols. No language restrictions were applied, provided that an English translation was available. We also screened the reference lists of relevant articles to identify additional studies.

Although causal inference cannot be established from a single observation, these findings support further evaluation of high-dose intravenous immunoglobulin in controlled clinical trials to define its role, optimal dosing, duration, and patient selection in long COVID. If confirmed, immunomodulatory strategies such as intravenous immunoglobulin can be a rational approach to restoring immune equilibrium for selected patients with severe, immune-mediated disease.

Contributors

Conceptualisation: MC, EPM, GDD, and EC. Writing original draft: MC, EPM, and GDD. Project administration: MC. Investigation: MC, VM, IM, CP, EC, EPM, SN, VB, GP, RC, SG, GDD, and CA. Resources: CDP and SM. Writing (review and editing): AA, FM, CA, EC, and EG.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Material

Contents

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Supplementary Table 1. Comparison of neuropsychological assessments: before and after treatment with COGPACK and IVIg.

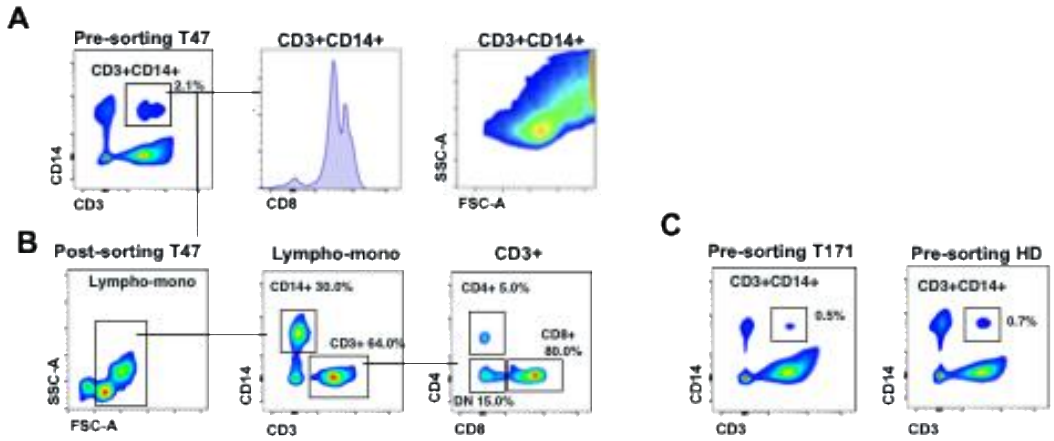
NPA	12th November 2024								04th November 2025						
	Row Score	Corrected Score	Equivalent Score (ES)						Row Score	Corrected Score	Equivalent Score (ES)				
			0	1	2	3	4				0	1	2	3	4
Global cognitive status									**Global cognitive status**						
MMSE	28	26.21							29	27.21					
Short-term memory/working memory									**Short-term memory/working memory**						
DSF	6	5.44				X			8	7.45					X
DSB	4	3.33			X				6	5.34					X
CSF	7	6.40					X		7	6.41					X
CSB	5	4.59					X		7	6.41					X
Episodic verbal memory									**Episodic verbal memory**						
RAVLT-ST	45	36.54				X			49	40.80				X	
RAVLT-RD	7	4.51	X						10	7.60				X	
RAVLT-REC	14 vs 1	0.95		X					14 vs 1	0.95		X			
ROCF-DR	24	16.17				X			22	14.39				X	
Language									**Language**						
PVF	23	12.39	X						33	22.47			X		
CVF	24	17.01					X		24	17.12					X
Speed of psycho-motor processing									**Speed of psycho-motor processing**						
DS	42	6			X				52	8			X		
TMTA	36	46				X			21	31.7					X
Attention									**Attention**						
MFTC-ACC	13 vs 0	1		X					13 vs 0	1		X			
MFTC-ERR	0						X		0						X
MFTC-T	65	87.91					X		36	58.43					X
Executive function									**Executive function**						
ST-T	13	21.52				X			11.5	19.55					X
ST-ERR	0						X		0						X
TMTB	53	92					X		33	76.25					X
Constructional praxis									**Constructional praxis**						
ROCF-C	36						X		36						X

COGPACK cognitive training performance across domains (attention/reaction, knowledge, memory, numerals/logic/geometry, speed of information processing, visuomotor functions, strategy/methodology, and special abilities). Two assessment sessions were conducted: (1) 12th Nov 2024; (2) 04th Nov 2025.

Abbreviations: Intravenous immunoglobulin (IVIg); Mini Mental State Examination (MMSE)(1); Rey Auditory Verbal Learning Test-Short Term (RAVLT-ST)(2); Rey Auditory Verbal Learning Test-Delayed Recall (RAVLT-RD)(2); Rey Auditory Verbal Learning Test-Recognition (RAVLT-REC)(2); Rey-Osterrieth Complex Figure- Delayed Recall (ROCF-DR)(3); Digit Span Forward (DSF)(3); Digit Span Backward (DSB)(3); Corsi Span Forward (CSF)(3); Corsi Span Backward (CSB)(3); Rey-Osterrieth Complex Figure- Copy (ROCF-C)(4); Multiple Features Target Cancellation-Accuracy (MFTC-ACC)(5); Multiple Features Target Cancellation-Errors (MFTC-ERR)(5); Multiple Features Target Cancellation-Time (MFTC-T)(5); Phonological Verbal Fluency (PVF)(6); Categorical Verbal Fluency (CVF)(6); Stroop test Colour Word- Time (ST-T)(7); Stroop test Colour Word- Errors (ST-ERR)(7); Trial Making Test A (TMTA)(8); Trial Making Test B (TMTB)(8); Digit Symbol Test (DS)(9); Beck Anxiety Inventory (BAI)(10); Beck Depression Inventory (BDI-II)(11); Beck Depression Inventory Somatic-Affective (BDI-II SA)(11); Beck Depression Inventory Cognitive (BDI-II C)(11).

*Raw NPA scores were adjusted for age, sex and education level, then converted into equivalent scores (ES)(12), using an ordinal scale ranging from 0 to 4 (ES=0 Deficient comprising; ES=1 Borderline performance; ES=2-3 Middle-lower comprising performance; ES =4 Middle-upper comprising performance).

Supplementary Figure A1. Flow cytometric analysis of $CD3^{+}CD14^{+}$ double-positive T-cell/monocyte aggregates



(A-C) Flow cytometric analysis of $CD3^{+}CD14^{+}$ double-positive T-cell–monocyte aggregates. Cells were stained with the Duraclone IM Phenotyping BASIC Tube (Beckman Coulter, Brea, USA) containing the following antibodies: CD45-Krome Orange, CD3- APC-A750, CD8-A700, CD4-APC, CD14-PC7, CD19-ECD, CD56-PE, and CD16-FITC. Cells were sorted with FACS Aria II (Beckton Dickinson, Franklin Lakes, USA). Analysis was performed with FlowJo version 10.10 (Beckton Dickinson, Franklin Lakes, USA). Analysis was performed on day 47 as it was known to have a high amount of spontaneous IFNγ and day 171 was chosen as it was known to have absent IFNγ.

(A) Pre-sorting profiles at T47 showing 2·1% $CD3^{+}CD14^{+}$ events, predominantly $CD8^{+}$ T cells and with high FSC-A and SSC-A.

(B) Post-sorting analysis, confirming separation of doublets in: CD14+, CD8+, CD4+, and double-negative T cells. Lines indicate the same population of cells before and after sorting.

(C) Comparative analysis of $CD3^{+}CD14^{+}$ cell frequency at late timepoint (T171) and one healthy donor, showing a marked reduction in double-positive events in the patient. FSC=forward scatter area. PBMC=peripheral blood mononuclear cell. SSC-A=side scatter area.

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